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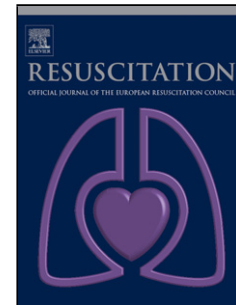
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TITLE PAGE

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Blowing hot or cold? Oxygenation and temperature after paediatric cardiac arrest.**Editorial**

Outcomes after out-of-hospital and in-hospital cardiac arrest (CA) in children continue to be poor (1,2). Hypoxia and ischaemia-reperfusion injury to the brain and other organs are the main causes of poor outcome. Search for evidence-based interventions to improve outcomes have met with limited success so far. Targeted temperature management (TTM), previously known as therapeutic hypothermia (TH), certainly lead the agenda with results of the Therapeutic Hypothermia After Pediatric Cardiac Arrest (THAPCA) trial expected soon (3). However, other modifiable factors in the 'post-cardiac arrest bundle of care' such as maintenance of normoxia, normocapnia, euglycemia, haemodynamic stability may be equally important and potentially synergistic in achieving good outcomes (4).

The ideal therapeutic range of oxygenation and appropriate concentration of fractional inspired oxygen (FiO_2) after return of spontaneous circulation (ROSC) have been a source of debate for more than two decades (5). A meta-analysis of animal studies recently concluded that administration of 100% oxygen therapy was associated with worse neurological outcome with a standardised mean difference of -0.64 (95% CI -1.06 to -0.22) (6). However paediatric models of cardiac arrest were excluded from the review. Use of air (21% FiO_2), rather than oxygen, is currently recommended for initial resuscitation of term infants (7). Interest in oxygen targets in post-CA adult survivors stemmed from the report of the Project IMPACT critical care database suggesting that arterial hyperoxia (defined by $\text{PaO}_2 > 300$ mm Hg) was associated with mortality (8). However, another study based on the analysis of Australia and New Zealand Adult Patient Database (ANZ-APD) published shortly after the initial report did not support this association (9). Since then there have been conflicting reports of association between partial pressure of oxygen (PaO_2) and outcomes after CA. A meta-analysis of published adult CA studies concluded that hyperoxia appeared to be correlated with increased in-hospital mortality of post-ROSC patients (10). However, caution

in applying these results to clinical practice was urged due to significant heterogeneity and limited number of studies analysed.

Aetiology of paediatric CA differs from adult and neonatal CA models. CA in adults is usually coronary artery disease related with sudden onset; in neonates, this is rare but may be related to perinatal events; whereas in children, this often follows respiratory insufficiency, hypoxia and acidosis. These significant differences prevent direct extrapolation of adult or neonatal evidence to paediatric population (11). Evidence for association between PaO_2 and outcomes after paediatric CA remains limited. A summary of paediatric literature relevant to this association is shown in Table 1. Despite lack of robust clinical evidence in children, current guidelines recommend targeting SaO_2 94-98% after ROSC with the aim of avoiding hyperoxia (4).

In this edition of *Resuscitation*, van Zelle and colleagues have explored the relationship between in-hospital mortality in a cohort of children admitted to PICU after CA and PaO_2 by cut-off points similar to the earlier paediatric reports as well as cumulative PaO_2 during the first 24 hours after ROSC over a 10-year period (12). They found that higher cumulative PaO_2 during 0-24 h and 6-24 h time periods was associated with better survival in children treated with TH (32-34°C) but not in others. van Zelle and colleagues have indeed provided a unique perspective in the debate about ideal oxygenation targets by utilising all available PaO_2 values during first 24 hours after CA to derive a marker for 'total oxygen dose'. In comparison, other paediatric studies have analysed exposure to hyperoxia as a dichotomous categorical variable based on presence or absence of values higher or lower than a target PaO_2 in early post-arrest period (Table 1). It is certainly intriguing, however, that the results of this novel analysis has yielded different results compared to that of meta-analyses of animal studies (6), adult cardiac arrest (10), paediatric studies (Table 1) (13-16) and a pilot randomised controlled trial comparing 30% oxygen versus 100% oxygen (17).

How might these differences be explained? The answer to this is perhaps complex. Firstly, does the beneficial effect of TH (32-34°C) counteract to a greater extent harmful effect of

hyperoxia or are they working synergistically? Reduction of free radical production and oxidative stress has been postulated as one of the physiological effects by which TH may modulate ischaemia reperfusion (18). While early protective effect of hypothermia on hyperoxic rather than normoxic re-oxygenation has been found in experimental animal studies (19), reports in humans have so far been contradictory (20). A potential future opportunity to explore this question will be an analysis of the THACPA trial database where one of these two variables (temperature) will have been controlled. We certainly do not yet know currently if we should be turning the oxygen up on patients treated with therapeutic hypothermia.

Secondly, several limitations exist and are mentioned within the report. In addition to those mentioned, it is uncertain whether the use of trapezoidal rule to estimate cumulative PaO_2 in the way the authors have done is ideal. Trapezoidal rule to estimate area under the curve (AUC) has been routinely used in pharmacokinetic research. As the authors allude to, it has also been used in estimation of AUC of glucose after a glucose tolerance test or in estimating resting metabolic rate etc. The common theme in all the above is that there is a pattern and predictability to the concentrations being measured. For example, elimination of most drugs follow first-order kinetics. But, variability in PaO_2 values can be quite marked and may occur within a matter of minutes. Pre-oxygenation for endotracheal tube suctioning, patient procedure, transport, variations in lung compliance, development of pulmonary oedema, variations in factors affecting oxygen dissociation curve may all produce fluctuations in PaO_2 . Depending on the number and timing of blood gases and whether the true peaks and troughs in PaO_2 were captured, one could over- or under-estimate the cumulative PaO_2 by manifold. While this does not render the analysis or its conclusions invalid, it remains an important limitation.

Thirdly, while increasing cumulative PaO_2 levels were found to improve survival, it is uncertain how a higher cumulative PaO_2 may be reached. It is also unknown whether the worse results in lower cumulative PaO_2 may be explained by exposure to varying degrees of

hypoxia. As shown in the report (12), brief periods of hyperoxia (>200 or 300 mm Hg by traditional cut-offs) may still result in relatively lower cumulative PaO_2 (Figure 3.b) whereas continuous mild hyperoxia ($200 < \text{PaO}_2 < 300$) without any period of hyperoxia (>200 or 300 mm Hg) may result in relatively higher cumulative PaO_2 (Figure 3.c). It is physiologically unlikely that all the above would have a similar effect on outcomes. A recent report from Pittsburgh, USA, found that while severe hyperoxia (>300 mmHg) was independently associated with decreased survival in adults; moderate or probable hyperoxia (100-299 mmHg) was not; and was instead associated with improved organ function at 24 hours (21). It is interesting that composite score of oxygen exposure (to reflect cumulative PaO_2) was analysed and found to be associated with improvement in organ function scores. It is quite possible that the relationship between PaO_2 and outcomes are non-linear especially when therapeutic hypothermia is used.

One of the main causes of poor outcomes after paediatric CA apart from death is neurological morbidity relating to hypoxic-ischaemic brain damage. Experimental models of asphyxial paediatric CA have shown that there was marked regional variability of cerebral oxygenation (22). Using partial pressure of brain tissue oxygen (PbO_2), it was found that cortical hypoxia appeared early, while thalamic hyperoxia was followed by normoxia. PbO_2 was also FiO_2 dependent. One other reason for better survival in this study may also be that the higher cumulative PaO_2 levels had a beneficial effect on PbO_2 .

The authors must certainly be commended on providing a fresh perspective on oxygenation thresholds to the continuing predicament facing clinicians and researchers alike. Future research into oxygenation thresholds should perhaps include 'total oxygen dose' as well as oxygen cut-offs in their analysis. However, clinicians managing post-CA paediatric survivors remain in a quandary. Given that the conclusions in this study (12) are based on a small subset of the original study and other limitations mentioned in this editorial and the article, it is best to view this report as hypothesis generating. Presence of significant differences in PaO_2 thresholds, time periods and the heterogeneous methodology in analysis in the studies

reported so far, comparisons between these studies cannot be robust. The solution to this problem is perhaps, to collect and publish standardised data from multiple clinical settings- i.e., uniform global reporting of paediatric cardiac arrest (23). But, this study adds more credibility to the presence of equipoise for conduct of randomised trials, or the very least comparative effectiveness studies based on robust prospective and systematic data collection, to inform the bundle of care required for post-CA paediatric survivors to achieve good neurological outcomes. Until then, resuscitating with 100% oxygen, then careful titration of FiO_2 to achieve and maintain normoxia, while aggressively avoiding hypoxia remains current best practice. Whether we blow hot or cold, still remains to be answered.

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Table 1: Summary of paediatric studies investigating association between PaO₂ and outcomes after cardiac arrest

First author	Number of patients/ Setting	Study method	PaO ₂ cut-off (mm Hg)	Frequency	Timing of PaO ₂	Outcome measure	Conclusion
Ferguson (13)	n=1875 IHCA & OHCA	Retrospective multi-centre	PaO ₂ ≥ 300 & as a continuous variable Hypoxia: <60	Single value	One hour post PICU admission	PICU mortality	Increased risk with hypoxia (higher) and hyperoxia but non- linear relationship
Del Castillo (14)	n=223 IHCA	Prospective multi-centre	PaO ₂ > 300 or PaO ₂ /FiO ₂ > 300 Hypoxia: <60	Two values	One & 24 hours post ROSC	In-hospital mortality	No significant difference
Bennett (15)	n=195 IHCA & OHCA	Retrospective multi-centre	PaO ₂ > 200 Hypoxia: <50	Multiple values ¹ Max & Min	First 6 hours post ROSC	Survival with good neurological outcome	No significant difference
Guerra- Wallace (16)	n=74 IHCA & OHCA	Retrospective single centre	PaO ₂ > 200 or 300 Hypoxia: <60	Multiple values ¹ . Max & Min	First 24 hours post ROSC	Mortality at 6- months	No significant difference

¹multiple values used only if more than one available. IHCA: In-hospital cardiac arrest, OHCA: Out-of-hospital cardiac arrest, ROSC, Return of spontaneous circulation. Max: Maximum, Min: minimum.